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Cancer Incidence Rate and Mortality Rate in Sickle Cell Disease Patients at Howard University Hospital: 1986–1995

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The incidence of cancer in patients with sickle cell disease (SCD) is not known. The 10-year follow-up data on 696 patients with SCD was analyzed at our institution in order to determine the cancer incidence and cancer mortality rates. The age range was 18 to 79 years, with a mean age of 28.8 years. There were 377 females and 319 males. The median follow-up was 3 years. Five patients developed cancer during this period. The cancer incidence rate was 5/2,864 or 1.74 per 1,000 patient years. The 95% CI was 0.64 to 4.32 per 1,000 patient years. There were 68 deaths with 3 being due to cancer. The cancer mortality rate was 3/2,873 or 1.04 cases per 1,000 patient years. Our data represent the first published paper that the authors are aware of, where the cancer incidence and mortality rates have been calculated for any group of patients with SCD. Am. J. Hematol. 55:188–192, 1997.

Key words: cancer incidence rate; mortality rate; sickle cell disease

INTRODUCTION

In 1986 Stricker and coworkers [1] reported four cases of hematologic malignancies in patients with sickle cell disease (SCD). They also reviewed the literature searching for all reported cases of hematologic malignancies in children and adults with SCD. Seventeen were found including four of their own. Because the denominator was not known, no attempt was made to determine incidence rate or mortality rate. Since then there have been no major reviews of this subject. However, multiple case reports [2–4] have documented both hematologic malignancies as well as solid tumors in patients with SCD. Baron et al [5] recently reported 117 African-American patients with renal cell carcinoma at their institution between 1952 and 1992 and three had SCD. The median age for the three patients was 36 years.

Based on the genotype frequency, this number was a 16.7-fold excess of SCD patients with renal cell carcinoma.

From our own review of the literature, we found no publications that report the incidence of malignant diseases in patients with SCD. Cancer incidence data in SCD are particularly important now that hydroxyurea is being used to decrease the frequency of pain crisis. The long-term implications for SCD patients taking hydroxyurea with respect to the development of malignancies are not known. Furthermore, allogeneic bone marrow transplantation is being explored as a treatment for SCD and this procedure may also be a risk factor for cancer development. Herein, we report five cases of malignant disease in sickle cell patients and we estimate the incidence and mortality rates for adult patients with SCD at our institution.

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TABLE I. Summary of Case Reports*

Case	Age	Sex	Hb Type	Cancer	Current	Hb/Hct	MCV	HbF
1	26	M	S-β^+-thal	Testicular	Alive	14.2/43.7	74	5.3
2	57	F	SS[a]	Poorly differentiated adeno CA of unknown prim	Dead	11.9/37.4	68	1.9
3	44	F	HbSC	Gastric	Dead	10.3/30.3	85.4	3.0
4	33	F	S-dβ-thal	Breast	Alive	6.5/19.7	98	15.1
5[b]	36	M	SS	NHL	Dead	9.9/28.7	104	14

*All patients were African-American. NHL, non-Hodgkin's lymphoma.
[a]Probable thal.
[b]HIV seropositive.

METHODS

In order to estimate the incidence of cancer in our population of adults with SCD, we used the Howard University Center for Sickle Cell Disease (HUCSCD) clinical activity databases for the calendar years 1986 to 1995. A total of 696 patients with SCD, who were 18 years or older and who were seen at our Center or at Howard University Hospital (HUH) during this 10-year period, had been entered in the yearly databases. The databases included fields for demographics and for clinical contact data such as clinic visits and hospitalizations. No patient was referred to the Sickle Cell Center because of a diagnosis of a suspicion of cancer.

Socioeconomic data for these patients were not available in the database. However, a review of their medical insurance showed that in recent years (1994 to 1995) 47% had Medicaid, 22.6% Medicare, 21.3% commercial insurance, and the rest miscellaneous sources of payment. For the cancer incidence calculations we assumed that if a patient appeared on a database even once for a given year, then that patient had been followed for the duration of that year. Similarly, if a patient appeared even once in each of two non-consecutive years, then the length of patient follow-up also included the intervening years. Descriptive statistics were used to determine patients' age, sex, and genotype. The cancer incidence rate [6] for our sickle cell patients was calculated as the number of new cancer cases divided by the number of patients followed from 1986 to 1995 times the individual number of follow-up years. The 95% confidence interval (CI) was calculated by the formula by Fleiss [7]. None of the patients had undergone bone marrow transplant, nor had any of the patients who developed cancer been treated with hydroxyurea. The Sickle Cell Center and its Director (OC) as well as two other authors of this paper (E.P. and J.K.) manage 95% of all adult sickle cell patients seen at our institution. Most patients had their primary care at the HUCSCD and age-appropriate recommended guidelines for cancer screening were followed. The Howard University Tumor Registry evaluates all charts of patients with cancer seen at this institution. The number of deaths for sickle cell patients (all causes) was 68, with an autopsy rate of 39.7%. We reviewed the hospital and office medical records of all patients with SCD and cancer for the study years, including their pathology report.

RESULTS

Case Reports (Table I)

Case 1. A 26-year-old African-American male with SCD (SB+-thal) was followed at the HUCSCD for more than 10 years. Seven years ago, he presented with a tender right testis. His physical examination revealed a right testicular mass. A radical orchidectomy was performed. A 3.2 × 2.1 × 1.8 cm mixed embryonal carcinoma and seminoma with occasional syncytial giant cells and focal lymphatic invasion was found. He was treated with cisplatinum, vinblastine, and bleomycin. The patient remains in complete remission 7 years after the cancer diagnosis.

Case 2. A 57-year-old African-American female with sickle cell anemia (SS) presented in 1991 with worsening anemia and shortness of breath. A chest X-ray revealed bilateral pleural effusion. A diagnostic and therapeutic thoracentesis revealed a poorly differentiated adenocarcinoma. After an extensive evaluation the primary site was indeterminate. Before treatment could be initiated, the patient developed lower extremity thrombosis and died suddenly. The immediate cause of death was thought to be pulmonary embolism. No autopsy was allowed.

Case 3. A 44-year-old African-American female with HbSC disease presented in 1990 with lower abdominal pain. An upper esophagogastroendoscopy revealed a 20 × 3.0 cm mass on the anterior wall of the prepyloric area of the stomach. Histologically the tumor was an ulcerated, poorly differentiated invasive adenocarcinoma. A colonoscopy found a tubulovillous adenoma. The patient went into acute renal failure (etiology unknown) and died before treatment for the adenocarcinoma was initiated. No autopsy was done.

Case 4. A 33-year-old female with sickle cell delta B thalassemia presented with a left breast mass in 1995. A

TABLE II. Cancer Incidence Rate by Age Group*

	Age group (years)			
	18–40	41–60	>60	All patients
Patients	293/327	25/46	1/4	319/377
Median follow-up (years)	3/3	2/3	3/4.5	3/3
Patient years	1,255/1,324	94/179	3/18	1,352/1,521
Patients with cancer	2/1	0/2	0/0	2/3
Cancer incidence +	1.6/.75	—/11.2	—/—	1.48/1.94

*Values represent male/female. +, per 1,000 patient years.

fine-needle aspiration biopsy specimen showed a poorly differentiated ductal carcinoma. Pathologic examination after a modified radical mastectomy revealed a tumor that was 9 cm in its largest dimension. Estrogen and progesterone receptors were not found. All lymph nodes were negative. No adjuvant chemotherapy was administered because of multiple organ damage that preceded her cancer diagnosis. She had dialysis dependent renal failure, transfusion dependent anemia, cardiomyopathy, and pulmonary hypertension. The patient is free of cancer more than 1 year after her cancer surgery.

Case 5. A 36-year-old homosexual HIV seropositive African-American male with sickle cell anemia (SS) was found to have a mass on the left shoulder in 1994. Immunohistochemical studies on the biopsied mass were positive for the Leucocyte Common Antigen (CD45) and Mature B-cells (CD20), consistent a B-cell, non-Hodgkin's lymphoma. He left our institution and died elsewhere before any cancer therapy was instituted.

Cancer Incidence and Mortality

Six hundred ninety-six adult SCD patients from HUH and HUCSCD were followed from their first visit for up to 10 years (1986–1995) (Table II). Their ages ranged from 18 to 79 years with a mean age of 28.8 years. Of these patients, 377 (54.1%) were female and they were followed for an average of 4.03 years. Three hundred nineteen (45.8%), were males who were followed for an average of 4.24 years. The median follow-up for the entire group was 3 years while average follow-up was 4.13 years. Twenty-three percent had sickle cell HbC disease, 66% had sickle cell anemia (SS), and 11% had other genotypes. Five patients (3 females and 2 males) developed cancer during this period. The mean age of the five patients with cancer was 39.2 years.

The cancer incidence rate among our SCD patients was 5/2,864 or 1.74 per 1,000 patient years. The 95% confidence interval for this estimate was 0.64 to 4.32 per 1,000 patient years. During the follow-up period, sixty-eight deaths were observed with three of these deaths being due to cancer. The cancer-specific mortality rate was, therefore, 3/2,873 or 1.04 cases per 1,000 patient years. No gender difference was observed in survival data analysis ($P = 0.21$). The cancer incidence rate for ages 18–40 was 1.6 per 1,000 patient years for males and 0.75 per 1,000 patient years for females. In the age range 41–60 years, there were no male deaths. However, the cancer incidence rate for females was 11.2 per 1,000 patient years. There were no cancer deaths for males or females who were older than 60 years. Females in the age group 41–60 years had the highest cancer incidence rate in any group, male or female.

DISCUSSION

Our data are unique in that we are unaware of any other studies where the cancer incidence and mortality rates have been estimated for patients with SCD. Data from a comparable cohort without SCD at our institution are not available so we could not compare our findings to that control group. Platt and co-workers [8] in a prospective study reported on the life expectancy and mortality risk in 3,764 patients with SCD. They reported four deaths from cancer: 1 breast, 1 ovary, 1 colon, and 1 multiple myeloma. However, these authors did not attempt to calculate cancer incidence or cancer mortality rates. For this reason, our SCD data on cancer incidence and mortality cannot be compared to those in Platt et al.'s study or to any other. The following discussion of published data on cancer statistics is not intended as a direct comparison. According to the American Cancer Society [9] the cancer incidence rate for all African-Americans during 1977–1983 was 382.8 cases per 100,000 population at risk or 3.82 cases per 1,000 population at risk. The corresponding cancer mortality rate for 1977–1983 was 209.8 cases per 100,000, or 2.1 per 1,000 population at risk. These data, while they offer some basis for discussion, do not represent an equivalent comparison. First, patient years (which we use as the denominator) are different from the population at risk. Second, the total population at risk in the American Cancer Society data includes subjects under 18 years of age. All of our patients were 18 years or older. Third, the duration of observation was different: 10 years for our SCD patients vs. 7 years for the general population. According to the SEER database [10], the age-specific cancer incidence rate for African-Americans between ages 35 to 44 years was 188.4 per 100,000 or 1.9 per 1,000 in 1990. This figure is comparable to that in our study with 1.74 per 1,000 patient years.

Attempting to establish an association between SCD and cancer is not new. Stricker et al. [1] concluded that there was no evidence to support a strong association between the two diseases based on his survey of published case reports: a total of 17 cases of SCD patients with malignancies. Their paper did not attempt to define the base population from which these cases were obtained. Pandit [11] suggests that the abnormal globin and its derivatives act as inhibitors and ''antibodies'' that

resist tumorigenesis. However, Stricker et al. [1] points out that the data from tropical Africa, where lymphoma, malaria, and SCD are significant public health concerns, would seem to refute Pandit's hypothesis. Indeed, others have suggested that patients with hematologic disorders are at a higher risk of developing hematologic malignancies. Moreover, Labi et al. [2] reported one case of bronchoalveolar carcinoma in a SCD patient and suggested that recurrent infection, inflammation, and fibrosis may contribute to a higher incidence of lung cancer. Also, as noted above, Baron et al. [5] reported what appears to be an inordinately high incidence of renal cell carcinoma in SCD seen at their institution between 1952 and 1992.

The issue of SCD and malignancy will need further clarification in light of the new and exciting changes in the management of patients with SCD. Charache et al. recently reported the results of a double-blind, randomized clinical trial, which demonstrated the efficacy of hydroxyurea in patients with SCD [12,13]. Hydroxyurea is now being used frequently in the management of patients with SCD. There may be a link between hydroxyurea and malignancy. Fruchtman et al. [14], for example, analyzed the Polycythemia Study Group data to assess the risk of acute leukemia transformation in patients with polycythemia vera (PCV) who were exposed to hydroxyurea. Fifty-one patients with PCV who were treated with hydroxyurea were compared to a historical control group. For patients taking the drug, 5.9% developed acute leukemia compared to 1.5% in the control group. However, the study population was small and statistical significance was not demonstrated ($P = 0.18$, logrank). Nand et al. [15] reported a 12% acute leukemia transformation in PCV patients taking hydroxyurea as the sole myelosuppressive agent. These data are similar to those reported by Weinfeld et al. [16] who noted 11% frequency of acute leukemia transformation in PCV patients. Non-Hodgkin's lymphoma is rare in PCV [17,18] patients. All patients who developed non-Hodgkin's lymphoma had been exposed to chlorambucil for 5 years or more. However, Hawkins and coworkers [19] reported one case of non-Hodgkin's lymphoma in a PCV patient treated with hydroxyurea alone. Only one case of a SCD patient with non-Hodgkin's lymphoma was reported in the last 10 years [20].

It is likely that patients with SCD treated with hydroxyurea would be on this therapy for longer periods (in many cases for life) than those in the Polycythemia Vera Study Group [15], who were followed for a median of only 8.6 years. Fruchtman et al.'s analysis [15] only included patients with acute leukemia. We do not know if other malignancies or cases of myelodysplastic syndrome were found in this study population. Downhower [21] has described chromosomal abnormalities in patients with lung cancer who were taking hydroxyurea. Charache et al. [14] has acknowledged the possibility that there may be tumorigenic potential in SCD patients taking this chemotherapeutic agent.

The Howard University Center for Sickle Cell Center and other institutions that participated in the Hydroxyurea Trial, are currently prospectively following patients treated with hydroxyurea for detection of long-term adverse effects including cancer. Now that we have estimated our cancer incidence rate here at Howard University, there will be a baseline from which to determine changes in cancer incidence and mortality rates since enrollment in the Hydroxyurea Trial.

Four of our 5 patients developed solid tumors. The exception was the fifth case who presented with HIV associated non-Hodgkin's lymphoma. It is well established that there is a strong association between HIV infection and non-Hodgkin's lymphoma. Therefore, it is possible that in this single case reported SCD alone was not a ''risk factor.'' It is remarkable, however, that in the years prior to 1985 when the HIV assay became routinely available, there was not a greater number of non-Hodgkin's lymphoma cases in SCD patients.

As the median age for SCD patient increases due to their improved medical care, it is also likely that the cancer incidence and mortality rates will increase. In the general population, the incidence of cancer increases with age. Whether there will be a ''triple risk'' of malignancy due to the presence of SCD, advancing age, and the use of hydroxyurea at this time is a matter of speculation.

In summary, we have reported the cancer incidence and mortality rates for adult patients with SCD at this institution. Our data are based on a limited population followed over 10 years. However, we believe the cancer incidence question needs to be evaluated further using a larger adult population base. We suggest that all centers where SCD patients are cared for should monitor these patients prospectively for the presence of cancer. Monitoring should also include laboratory investigation for cytogenetic changes.

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